PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing (day/month/year)	28.04.2000
REPLY DUE	within 2 month(s) from the above date of mailing
Applicant's or agent's file reference	P019092WO
International application No.	PCT/IB99/00844
International filing date (day/month/year)	27/04/1999
Priority date (day/month/year)	27/04/1998
International Patent Classification (IPC) or both national classification and IPC	C07K14/33
Applicant	CHIRON S.P.A. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☒	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27/08/2000.

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Form PCT/IPEA/408 (cover sheet) (January 1994)

WRITTEN OPINION

International application No. PCT/IB99/00844

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-58 as originally filed

Claims, No.:

1-32 as originally filed

Drawings, sheets:

1/14-14/14 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

WRITTEN OPINION

International application No. PCT/IB99/00844

3. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4, 8, 9, 17-30, 32
Inventive step (IS)	Claims	1-32
Industrial applicability (IA)	Claims	22 (reserved opinion)

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/IB99/00844

II. PRIORITY

1) This first preliminary written opinion has been established after consideration of the priority document GB 9808932.9 of 27.04.98 . Therefore, document WO 98 43677 published 08.10.98 cited in the International Search Report are not relevant in establishing the novelty of the present invention.

V. REASONED STATEMENT UNDER RULE 66.2 (a) (ii)

2) The present application relates to the generation of carrier proteins comprising a number of CD4+ cell epitopes. Said proteins are meant as conjugants to capsular polysaccharides, originating from encapsulated bacteria. So conjugated polysaccharide antigens, are immunogenic and capable of eliciting a T-cell dependent immune response, thus, transforming T-cell independent polysaccharide antigens into T-cell dependent antigens useful in the preparation of conjugate vaccines suitable for protection of young children.

3) The subject-matter of **Claim 1** is not novel as required by Article 33(2) PCT.

Said claim relates to a carrier protein comprising at least five CD4+ T-cell epitopes. Documents:

D1: THOMSON S A ET AL. in JOURNAL OF VIROLOGY, vol. 72, no. 3, March 1998 (1998-03), pages 2246-2252;

D2: EP-A-0 429 816 , 5 June 1991;

disclose proteins comprising at least five CD4+ T-cell epitopes and which contain information for carrier function. Therefore the subject-matter of said claim is not novel.

Similarly, the subject-matter of **Claims 2, 3, 8, 17-30, 32** is not novel either.

4) Document D2, in particular, discloses a conjugate (Ac-Cys-$(NANP)_3)_{35}$-TT which comprises the multiple copies of the immunodominat B cell epitope of Plasmodium falciparum circumsporozoite (CS) and the full length tetanus toxoid (TT) protein. This conjugate comprises at least five different CD4+ epitopes from the TT and CS epitope. Thus, document D2 is novelty destroying for the subject-

matter of **Claims 4, 9**.

5) The subject-matter of **Claims 5-7, 10-16, 31** is not inventive as required by Article 33(3) PCT.

(i) **Claim 5** relates to a carrier protein comprising the following CD4+ epitopes: P23TT, P32TT, P21TT, PfCs, P30TT, P2TT, HBVnc, HA, HbsAg, MT.

Document D2 discloses a carrier protein comprising all the CD4+ epitopes from TT and the immunodominant epitope from CS. As mentioned in the description of the present application on page 5: "other suitable carrier peptide epitopes will be known to those of skill in the art", indicating that the selection of particular CD4+ epitopes falls within the customary practice of skilled persons. Thus, the subject-matter of **Claims 5-7, 10** lack an inventive step.

(ii) The subject-matter of **Claim 11** relates to a carrier protein as presented above, conjugated to a polysaccharide.

Documents:
D3: PARADISO, PETER R. ET AL. in VACCINE RES. (1993), 2(4), 239-48 , vol. 2, no. 4, 1993, pages 239-248;
D4: DE VELASCO E A ET AL. in INFECTION AND IMMUNITY, vol. 63, no. 3, March 1995 (1995-03), pages 961-968;
disclose carrier proteins conjugated to polysaccharides and the production of conjugate vaccines. Thus, the skilled person will combine the teachings of document D2, disclosing the carrier protein, with the teachings of any of D3 or D4, disclosing conjugates with said carrier protein and uses thereof, and he will arrive at the subject-matter of **Claims 11-16, 31** without exercising any inventive skills.

Similarly, the subject-matter of **Claims 17-30, 32** is not inventive either.

6) For the assessment of the present **Claim 22** as far as it is directed to a method of treatment of the human or animal body or to a diagnostic method practised on the human or animal body, no unified criteria exist in the PCT, on the question whether they are industrially applicable. The patentability can be dependent upon

the formulation of the claims.

VI. CERTAIN DOCUMENTS CITED

7) The following documents are cited under Rule 70.10 PCT
WO 98 43677, published 08.10.98

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION

8) The Applicant is reminded that the claims must be comprehensible from the technical point of view and indicate all the essential features necessary to perform the invention (Rule 6 PCT). The subject-matter of **Claims 1-3, 8, 10-32** does not fulfil this condition. Said claims are drafted as the result to be achieved, i.e. they state the technical problem rather than disclosing the technical features essential for the solution of the problem. Such a feature in the present case would be the CD4+ T cell epitopes comprised in the claimed protein.

9) Furthermore, dependent **Claims 4-7, 9** do not clearly specify the claimed subject-matter contrary to the requirements of Article 6 PCT. The claimed epitope or protein is only defined by an arbitrary designation, namely "P23TT, P32TT, P21TT, PfCs, P30TT, P2TT, HBVnc, HA, HbsAg, MT, hsp70, N6, N10 or N19" without disclosing any technical feature which unambiguously characterizes the claimed subject-matter. An epitope or a protein being a chemical product should be clearly defined by its formula i.e. its amino acid sequence as for example shown on Table I page 36 and Figures 1, 2 and 8.

Special note is made to the fact that an epitope with the name "PfCs" is not disclosed by the description, thus, the subject-matter of **Claims 4-7** does not meet the requirements of Article 5 PCT.

10) The vague and imprecise statement "incorporated herein by reference" in the description, on page 31 for example, implies that the subject-matter for which protection is sought may be different than that defined by the claims, thereby, resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, PCT/GL/3 III, 4.3a).

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Correspondence with the EPO on PCT Chapter II demands

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